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Research Article

Haematopoietic Cell Transplants in Adults Acute Lymphoblastic Leukaemia in a Resource-poor Middle East Country

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Keywords: Stem cell transplantation; ALL; Resource-poor countries; Jordan

Abstract

Background: Outcomes of chemotherapy in adults with ALL in resource-poor countries are reportedly worse compared with outcomes in resource-rich countries. There are few comparative data on transplants in these settings.

Methods: Retrospective analysis of 102 consecutive subjects > 18 years with ALL receiving an allotransplant from Jan 2007 to Sept 2022 in Jordan.

Results: Median follow-up is 38 mo ([IQR] 16-80 mo). 81 subjects were men. The median age was 29 y(IQR 22-36 y). 63 were B-cell and 38, were T-cell lineage. 31 had the Ph-chromosome. 68 were in 1st and 34, ≥ 2nd histological complete remission. 97 received intensive conditioning. Donors were an HLA-identical sibling (N = 88) or an HLA-mis-matched relative (N = 14). Grafts were blood cells. Subjects received conventional GvHD prophylaxis, cyclophosphamide (N = 11) or ATG (N = 3). All subjects recovered bone marrow function with complete donor chimerism. 5-year leukemia-free survival (LFS), 58% (47, 69%) and survival, 45% (34, 56%). 45 subjects developed acute and 44, cGvHD. 3-year cumulative incidence of cGvHD was 28% (15, 42%). 5-year CIR was 32% (18, 45%) and 3-year NRM, 25% (15, 35%).

Conclusion: Allotransplant outcomes in adults with ALL in Jordan, a resource-poor country, seem comparable to those reported in resource-rich countries.

Introduction

Allogeneic haematopoietic cell transplants (alloSCTs) are an important therapy for high-risk and advanced adult acute lymphoblastic leukemia (ALL) [1-6]. Two systematic reviews showed that alloSCT was considered the best option for adult subjects with ALL in first complete remission (CR1) with high-risk features. In addition, HLA-matched siblings (MSD) or matched unrelated donors (MUD) were the preferred donor type in this setting [2,3]. The introduction of novel immunotherapy agents like blinatomumab, innotuzumab, and chimeric antigen receptor T-cells (CART), greater availability of alternative donors, and novel preparative conditioning regimens have certainly altered the treatment landscape of ALL [7-14]. Most of the immunotherapy drugs and CAR T cells are not available in Jordan.

Outcomes of chemotherapy in adults with ALL are reportedly worse in resource-poor compared with -rich countries [15-18]. There are few data comparing allotransplant outcomes in these settings [19-21]. We aimed to report on allo-SCT in ALL patients from poor-resourced

countries and indirectly compare with results in rich countries. It is worth mentioning that treatment for patients with ALL and Transplants in Jordan was funded uniformly by the Royal Hashemite Court and the Jordanian Ministry of Health across all socio-economic classes. We report outcomes of 102 consecutive adults with ALL transplanted in Jordan, which seem comparable to those reported from resource-rich countries.

Methods

Subjects, study design, and endpoints

We used the Bone Marrow Transplant Program Registry of King Hussein Cancer Center (KHCC) to identify 102 consecutive subjects > 18 years receiving a 1st allotransplant from January 2007 to September 2022. The diagnosis was based on the World Health Organization criteria [21]. Indications for transplant, pretransplant preparative regimen, and supportive care were managed according to protocols at King Hussein Cancer Center (KHCC). A related HLA-haplotype-mismatched donor was defined as one with ≥ 2 HLA mismatches with the recipient. Pretransplant measurable residual disease (MRD) was assessed by multi-parameter flow cytometry (MPFC) [22-24]. The intensity of pre-transplant conditioning was defined as published [20]. Neutrophil recovery was defined as a neutrophil concentration > 0.5x10E+9/L for 3 consecutive days. Primary graft failure was defined as failure to achieve this milestone for 3 consecutive days by day 28 [21]. Acute and chronic graft-*versus*-host-disease (G*v*HD) are diagnosed as described [25,26]. The Institutional Review Board (IRB) of King Hussein Cancer Center (KHCC) approved the study and waived the informed consent.

Statistics

Quantitative baseline variables were described as median and qualitative described as numbers and percentages. To compare quantitative variables between groups, the Wilcoxon rank sum test will be used, and qualitative variables by the Chi-square test or Fisher exact test. Leukemia-free survival (LFS) was defined as the interval from transplant to relapse with survivors in remission censored at withdrawal of consent or last follow-up. Survival was defined as the interval from transplant to death from any cause with survivors censored at the last follow-up. LFS and survival will be estimated using the Kaplan-Meier method. Non-relapse mortality (NRM) and Cumulative Incidence of relapse (CIR) were calculated using a competing risk model [27]. Incidences of acute and chronic G*v*HD were estimated considering relapse and NRM as competing risks [28]. Cox proportional hazard regression was used in uni-variable analysis (MVA). Statistical analyses used SAS version 9.4 (SAS Institute Inc, Cary, NC, USA). *p* -values are 2--2-sided and considered significant when < 0.05.

Results

Subject-, disease- and transplant-related co-variates

Subject-disease- and transplant-related co-variates are displayed in Table 1. Whereas, 81 subjects were men. Median recipient and donor ages were 29 years Interquartile Range [IQR] of 22-36 years and 28 years ([IQR] 21-35 years). Here, 63 leukaemias were B-cell and 38, T-cell lineage ALL. 31 subjects had the Ph-chromosome. 68 subjects were in 1st and 34 in ≥ 2nd histological complete remission. Indication for transplant

Table 1: Subject-, disease- and transplant-related co-variates.

Variable		Number (%)
Gender	Female	21(21%)
	Male	81(79%)
Presentation	De novo ALL	74(72.5%)
	Relapsed ALL	28(27.5%)
Cell of origin	B-cell ALL T-cell ALL Biphenotypic leukemia	63(62%) 38(37%) 1(1%)
Bcr-Abl by RT-PCR	Negative	71(69.6%)
	Positive	31(30.4%)
Karyotyping	Abnormal Diploid Hyperdiploidy Missed/unavailable	32(31.4%) 41(40.2%) 14(14%) 29(28.4%)
Pre-transplant MRD by 10-color flowcytometry	Positive Negative Missed/unavailable	13(13%) 73(72%) 16(15%)
Pre-transplant MRD by RT-PCR	Negative Positive Missed/unavailable	73(71%) 2(2%) 28(27%)
Disease status	CR1 ≥ CR2	68(67%) 34(33%)
Donor type	Matched sibling HLA-mismatched relatives	88(86.3%) 14(13.7%)
Recipient CMV serostatus	Positive Negative	101(99%) 1(1%)
Donor CMV seroststus	Positive Negative	97(95%) 5(5%)
Stem Cell Source	Peripheral blood	100(98%)
G*v*HD Prophylaxis	Calcineurin inhibitor / Methotrexate Calcineurin inhibitor/ Mycophenolate Calcineurin inhibitor/ Mycophenolate / Posttranspalnt cyclophosphamide	86(84%) 5(5%) 11(11%)
Conditioning intensity	Myeloablative	97(95%)
	Reduced intensity	5(5%)
Conditioning regimen	Total body irradiation-based	96 (94%)
	Others	6(6%)
Day-100 non-relapse mortality (n-14)		8(57%)
Disease status at last encounter	Remission Relapse	68(67%) 34(33%)
Patient status at last encounter	Alive	52(51%)
	Dead	50(49%)

ALL: Acute Lymphoblastic Leukemia; RT-PCR: Reverse Transcriptase-Polymerase Chain Reaction; MRD: Measurable Residual Disease; CR: Complete Remission; CMV: Cytomegalovirus; CNI: Calcineurin Inhibitor; MMF: Mycophenolate Mofetil; PTCy: Post-transplant Cyclophosphamide; ATG: Anti-Thymocyte Globulin; aGvHD: Acute Graft-versus-Host Disease; cGvHD: Chronic Graft-versus-Host Disease; NRM: Non-Relapse Mortality.

in 1st CR was based on age, initial WBC cytogenetics, and a positive MRD test in remission after induction. 97 received intensive pretransplant conditioning, with total body radiation (N = 95) or busulfan (N = 2). Five received reduced-intensity pretransplant conditioning. Donors were HLA-identical siblings in 88 and HLA-mismatched relatives in 14. All grafts were blood cells. 86 subjects received calcineurin inhibitors, cyclosporine (CSA), or tacrolimus (TAC), with methotrexate (N = 6) or mycophenolate mofetil (MMF; N = 5) for graft-*versus*-host-disease (G*v*HD) prophylaxis, 11 posttransplant cyclophosphamide and 3, anti-thymocyte globulin (ATG). Pretransplant MRD state was available in 86 subjects, negative in 57, -positive in 13, and missing/ not available in 16. The median time to transplant in 1st remission was 6 months (Range, 2-13 mo), and from relapse to transplant, 8 months (Range, 2-74 mo).

Outcomes

The median follow-up of survivors is 38 months (Interquartile Range [IQR], 16-80 months). The median interval to neutrophil recovery was 14 days (Range, 11-22 days) and to platelet recovery, 17 days (Range, 10-47 days). There was no graft failure among evaluable subjects. 100-day deaths were 10% (95% Confidence Interval [CI], 4, 16%). 3-year non-relapse mortality (NRM) was 25% (15, 35%). 5-year cumulative incidence of relapse (CIR) was 32% (18, 45%), LFS, 58% (47, 69%), and survival, 45% (34, 56%) as shown in Figure 1. Uni- and multi-variable analyses of LFS and survival are displayed in Table 2. Pretransplant remission state (P = 0.001), negative MRD-test during histological complete remission (p = 0.012), acute G*v*HD (p = 0.009), and chronic G*v*HD (p = 0.03) were associated with better LFS whereas TBI-based pretransplant conditioning was associated with better survival p = 0.006).

45 subjects developed acute G*v*HD which was ≥ grade-2 in 29 and ≥ grade-3 in 3. 44 subjects developed chronic G*v*HD, which was moderate to severe in 35. The cumulative incidence of chronic G*v*HD was 28% (15, 42%) at 3 years. There was no significant difference in cumulative incidences of acute or chronic G*v*HD based on donor type, donor or patient age, and pretransplant conditioning intensity (All p-values > 0.10).

50 subjects died. Relapse was the most common cause of death (N = 27) followed by infections (N =17), G*v*HD (N = 5), interstitial pneumonia (N = 2), and coronavirus infectious disease-2019 (CoVID-19; N =1).

Discussion

Results of transplants for adults with ALL in Jordan seem similar to those reported from resource-rich countries as shown in Table 3. Goldstone, et al. (MRC UKALL XII/ECOG E2993) reported 5-year cumulative incidences of relapse (CIR) of 24% in standard risk and 37% in high-risk subjects and survival of 53% (48, 58%) [29]. Cornelissen, et al. reported 5-year CIR of 24% (23, 60%), disease-free survival (DFS) of 60% (41, 89%), and survival of 61% (46,100%) [30]. Ribera, et al. reported (ALL-HR-11) reported 5-year CIR 43% (36, 50%), event-free survival (EFS) 40% (34, 47%), and survival 49% (42, 56%) [31]. The Acute Leukemia Working Group of the European Bone Marrow Transplantation Registry Study reported a 2-year CIR of 26% (52, 83%), LFS of 51% (46, 56%), and survival of 59% (53, 64%) [5].

There are a few studies from resource-poor countries. A dedicated registry study addressing transplant outcomes in the region is lacking. Silva, et al. reported data from 275 subjects in Brazil. 5-year CIR was 28% (23, 34%), LFS, 38% (32, 44%) and survival, 41% (35, 47%) [20]. El-Cheikh, et al. reported data from 25 subjects in Lebanon who received first allotransplants. 3-year LFS of 82.5% compared to 51% (P-0.592) and OS of 89% compared to 55% for non-allo-SCT patients (P-0.036) [18]. In the lack of novel therapies and allo-

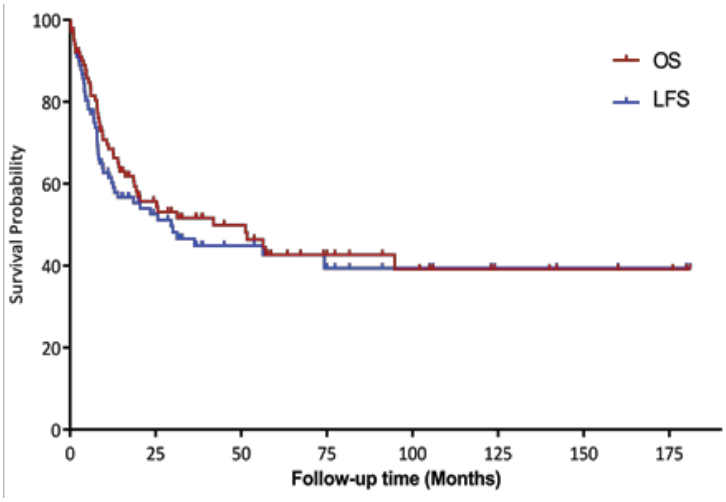

Figure 1: Leukemia-free survival (LFS) and survival.

Table 2: Uni- and multi-variable analyses of Leukemia-free survival (LFS) and survival

Uni- and multivariate analyses regression for OS		UVA HR(95% CI)	*p* -value	MVA HR(95% CI)	*p* -value
Recipient age group	Age < 35 *vs.* ≥ 35	0.86 (0.47, 1.58)	0.6342		
Recipient Gender	Female *vs.* male	0.60 (0.28, 1.27)	0.1776		
Cell of origin	B-cell *vs.* T-cell	1.25 (0.70, 2.21)	0.4524		
Disease status at transplant	CR1 *vs.* ≥CR2	1.32 (0.75, 2.32)	0.3371		
Pre-transplant MRD by Flow	Negative *vs.*Positive	0.56 (0.28, 1.15)	0.1088		
Pre-transplant Phil by PCR	Negative *vs.* Positive	1.22 (0.67, 2.22)	0.5196		
Conditioning intensity	MAC *vs.* RIC	0.94 (0.23, 3.89)	0.9319		
Conditioning regimen	TBI-Based *vs.* others	1.65 (0.51, 5.32)	< 0.001	1.567(0.486-5.050)	0.0061
Stem Cell source	Bone marrow *vs.* peripheral blood	NA(NA, NA)	0.5544		
aGvHD	Yes *vs.* No	1.69 (0.95, 3.02)	0.0723		
cGvHD	Yes *vs.* No	1.80 (1.02, 3.15)	0.0384	1.741(0.988, 3.068)	0.0552
cGvHD NIH score (*n* = 44)	1 *vs.* 2 or 3	1.44 (0.52, 3.98)	0.4771		
Uni- and multivariate analyses regression for EFS		UVA HR(95% CI)	*p* -value	MVA HR(95% CI)	
Recipient age	< 35 *vs.* ≥ 35	0.99 (0.55, 1.76)	0.9660		
Gender	Female *vs.* Male	0.75 (0.38, 1.49)	0.4092		
Cell of origin	B-cell *vs.* T-cell	1.45 (0.83, 2.52)	0.1852		
Disease status at transplant	CR1 *vs.* ≥ CR2	1.56 (0.91, 2.66)			
Pre-transplant MRD by flow	Negative *vs.* positive	0.50 (0.25, 1.01)	0.0489	0.525(0.254-1.084)	0.0816
Pre-transplant Phil by PCR	Negative *vs.* positive	1.27 (0.71, 2.26)			
Conditioning intensity	Myeloabaltive vs Reduced intensity	1.14 (0.28, 4.68)	0.8588		
Conditioning regimen	TBI-Based *vs.* others	1.45 (0.45, 4.65)	< 0.001	1.731(0.520-5.760)	0.0098
Stem Cell source	Bone marrow *vs.* peripheral blood	NA (NA, NA)	0.5002		
aGvHD	Yes *vs.* No	1.97 (1.12, 3.45)	0.0156	1.933(1.014-3.686)	0.0454
cGvHD	Yes *vs.* No	1.80 (1.05, 3.07)	0.0302	1.500(0.797-2.824)	0.2089
Uni- and multivariate analyses regression for LFS		UVA HR(95% CI)	*p* -value	MVA HR(95% CI)	*p* -value
Recipient age	< 35 *vs.* ≥ 35	1.29 (0.58, 2.84)	0.5291		
Recipient Gender	Female *vs.* Male	0.89 (0.39, 2.05)	0.7878		
Cell of origin	B-cell *vs.* T-cell	1.10 (0.56, 2.17)	0.7819		
Disease status at transplant at transplant	CR1 *vs.* ≥ CR2	2.17 (1.11, 4.22)	0.0196	3.679(1.644-8.233)	0.0015
Pre-transplant MRD by flow	Negative *vs.* positive	0.37 (0.15, 0.88	0.0196	0.318(0.129-0.785)	0.0129
Pre-transplant Phil by PCR	Negative *vs.* positive	1.98 (0.86, 4.53)	0.0999		
Conditioning intensity	Myeloabaltive *vs.* Reduced intensity	1.40 (0.19, 10.27)	0.7391		
Conditioning regimen	TBI-Based *vs.* others	0.76 (0.10, 5.57)	0.7872		
Stem Cell source	Bone marrow *vs.* peripheral blood	NA(NA, NA)	0.6516		
aGvHD	Yes *vs.* No	2.59 (1.21, 5.53)	0.0108	3.379(1.341-8.513)	0.0098
cGvHD	Yes *vs.* No	1.93 (0.97, 3.84)	0.0566	1.841(1.035,3.275)	0.0377

Table 3: Studies of allotransplants in adult ALL in resource-rich, and poor countries.

Study reference	Transplant type	LFS	CIR	NRM	OS	95% CI	*p* -value
[29] (n-1929) UK	MSD-CR1	----	SR-ALL:24% *vs.* 49% HR-ALL:37% *vs.* 63%	SR-ALL 7% *vs.* 19.5%	5-year 53%; 5-year 45%	48% - 58% 40% - 49%	0 .01
[30] (n-422) Netherlands	MSD-CR1	60% *vs.* 42%; P .01	24% *vs.* 55%; P- 0.001	HR-ALL 13.6% *vs.* 35.6%	5-year 61 *vs.* 47%	0.46-1.05	0.08
Ribera, et al. 2005 (n-324) Spain	MSD	5-year 35% (95% CI, 30%-41%)		P 0.002	5-year 34%	28% - 39%	
[5] (n 2304) EBMT	Haplo vs MSD CR1, CR2	2-year 55.4% *vs.* 51% (P-0.07)	26% *vs.* 31.6% P-0.017		2-year 58.8% *vs.* 67.4%	53.3%– 63.9% 64.8%– 69.8%	< 0.001
Brissot, et al. 2020 (n-615) EBMT	MUD, MMUD, Haplo, CBT-CR2	30.5-39.6%	32.6-37.6%	22.9% *vs.* 13%		38.3-47.2%	
Kaito, et al. 2022 (*n* = 382) Japan	MSD, MUD, CBT CR2 *vs.* CR1	42.9% *vs.* 64.0%; *p* < .001	34.2% *vs.* 17.6%; *p* < .001	*p* < 0.001	3-year 51.8% *vs.* 68.1%	46.4-57.0 *vs.* 65.4-70.6	< 0 .001
[20] (n-275) Braziel	MSD/MMSD/MUC/ Haplo/CBT	5-year 37.8% (95% CI:2.3-44.1)	5-year 28.1% (95% CI: 22.9-33.6%)	5-year 34.1% (95% CI: 2 8.4 39.8%)	5-year 34.1%	95% CI: 28.4%-39.8%)	
[18] (n-62) Lebanon	Allo-SCT *vs.* No allo-SCT	82.5% *vs.* 50.5% ' P-0.592			88.9% *vs.* 54.8%		0.036
[6] CIBMTR N-3892	Haplo *vs.* MRD Haplo *vs.* MUD	1.22(1.03 0.88); P-.71 1.03 (0.87-1.22) .73	0.99(0.81-1.21) P- .93 0.83(0.67-1.03) P- .09	1.06(0.81-1.41) P-.66 1.42(1.07-1.89) P-.02		1.13(95% CI : .94-1.36) 1.17(95% CI: 0.96-1.41)	0.11 0.11

SCT in most cancer centers in our region, our results might be used as a reference for future multinational multicenter registry studies using allo-SCT and might be included in regional clinical practice guidelines.

Our study has several limitations including small sample size and heterogeneous disease, subject- and transplant-related co-variates. Comparison of our results with those of other studies without subject-level data is problematic.

Conclusion

In conclusion, results of transplant in adults with ALL in Jordan, a resource-poor country, seem comparable to those reported in resource-rich countries.

Statements and declarations

Study approval statement: The study was approved and the consent was granted exemption by the Institutional Review Board (IRB) of King Hussein Cancer Center (KHCC).

Conflict of interest: RPG is a consultant to Antengene Biotech LLC; Medical Director, FFF Enterprises Inc.; A speaker for Janssen Pharma and Hengrui Pharma; Board of Directors: Russian Foundation for Cancer Research Support and Scientific Advisory Board, StemRad Ltd.

Data sharing: Available on request from the corresponding author.

Author's contributions: KH designed the study and wrote the first draft and final typescript, IM, LH, and MK extracted the data, WD contributed to data collection; HA cleared the data, AA and AT did complete data analysis, NK, NA, and FB edited the initial draft and provided feedback, RPG edited the final typescript. The authors approved the final typescript, took responsibility for the content, and agreed to submit it for publication.

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